or redundant orientational cue for adult birds. The accurate orientation of caged migrants under stationary planetarium skies supports this view (*11*).

This hypothesis does not explain why the young migrant orients southward on its first flight. Rotation seems merely to provide a stable reference axis. The use of this reference to select a southerly heading in preference to any other remains a topic for future investigation.

This study demonstrates the complexity involved in the maturation of one orientational system available to indigo buntings. Undoubtedly, the picture will become more complex as we learn more about additional components of avian guidance systems.

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Circulating Immunoglobulin M: Increased Concentrations in Endemic and Sporadic Goiter

Abstract. *Increased concentrations of immunoglobulin M have been found in the circulation of approximately half of patients with either endemic or sporadic nontoxic goiter. Blood was obtained from patients in several iodine-deficient goitrous areas; the patients with sporadic goiter resided in or about New York City. Concentrations of immunoglobulins G, A, and D were normal. Blood for control purposes was taken from patients residing in cities near the goiter areas where there was no iodine deficiency, and in New York City. Most of these samples came from hospitalized patients without known thyroid disease and were collected at random. Chi-square values for the difference between the number of goitrous patients with elevated concentrations of immunoglobulin M and those in the control patients were highly significant statistically.*

Endemic goiter remains one of the world's most prevalent diseases. Iodine deficiency is accepted as the precipitating factor, if not the cause, of most endemias (*1*), although a variety of other factors underlying the goitrogenesis have been suggested. Apart from McCarrison (*2*), the concept that infection might be implicated in goitrogenesis has not found much support, except for the demonstration of bacterial pollution in the water of two goitrous areas (*3*). The possibility that an autoimmune process might be operative in endemic goiter has been raised by the observations in two studies that in about half of patients antibody titers to thyroglobulin were increased (*4, 5*) although in a third study this could not be shown (*6*). No particular increase in antibody titers to thyroglobulin has been described in patients with sporadic goiter.

The results of our study reveal that approximately half of patients with either endemic or sporadic goiter had increased concentrations of circulating immunoglobulin M (IgM) whereas only 10 percent or fewer of appropriate controls had increased IgM. There was no corresponding increase in circulating concentrations of immunoglobulin G, A, or D (IgG, IgA, IgD).

Immunoglobulin concentrations were determined by single radial immunodiffusion (*7*). Plates were obtained commercially from Kallestad Laboratories, Inc. The specificity of the antiserums for IgG and IgM, respectively, was checked in two separate trials. No cross-reactions were elicited by IgG placed in the wells of the plate containing antiserum to IgM or by IgM placed in the plate containing antiserum to IgG. Serums for the most part were stored frozen at − 20°C. Serum specimens sent from abroad were preserved by the addition of merthiolate in a 1 : 10,000 concentration except those from Finland and Ecuador. These were lyophilized but not otherwise treated prior to being shipped by air freight.

Serums from areas endemic for goiter were collected as follows: healthy goitrous and nongoitrous patients in the iodine-deficient areas of the Åland Islands, Finland; apparently healthy goitrous subjects from Fourna, Evritania, a mountainous village outside Athens, Greece; and, through the cooperation of Dr. Albrecht Foldenauer, a small series each from healthy goitrous subjects from an endemic area near Munich, Germany. Serums also were obtained from a group of cretins living in two villages in an iodine-deficient area of Ecuador, La Esperanza and Tocachi, through the courtesy of Drs. R. Fierro-Benitez and J. B. Stanbury.

Serums from patients with sporadic nontoxic nodular goiter were kept at −20°C until used (mostly within 1 to

Table 1. Concentrations of IgM in serums of control subjects and of patients from endemic goiter areas.

Location	IgM titers	
	>180 mg/ml (No.)	<180 mg/ml (No.)
Control subjects		
New York	10	99
Greece (D. Koutras)	4	22
Finland (P. Wahlberg)	2	23
Total	16	144
Goiter patients		
Greece (D. Koutras)	10	10
Finland (P. Wahlberg)	10	6
Germany (A. Foldenauer)	5*	10†
Cretin patients		
Ecuador (R. Fierro-Benitez and J. B. Stanbury)	11	11
Total	25 (+11)	26 (+11)

* Four untreated; one treated. † Six untreated; four treated.

Table 2. Chi-square values in endemic goiter. The chi-square test yields P values of $<.001$ with limits of 200 mg per 100 ml and 160 mg per 100 ml.

	IgM titers			
	> 180 mg/ml (No.)	< 180 mg/ml (No.)	χ^2	P
I (Total endemic)	36	37		
II (Greek and Finnish controls)	6	45	18.69 (I from II)	< .001
III (Total controls)	16	144	47.21 (I from III)	< .001

2 weeks). As controls, bloods were obtained from a group of healthy subjects, and two groups of hospital patients without known thyroid disease, all living in or near New York City; from a group of healthy subjects in Mariehamn in the Åland Islands; and from two groups of hospital patients without known thyroid disease, also in areas of iodine abundance, namely Athens and Munich. Age and sex distributions were essentially the same in all patient and control groups, except that there were no available control serums from the area of cretinism. Parasitism and nutritional problems exist in Ecuador; but no overt disease other than goiter was recognized by the physicians in the various areas of iodine deficiency. We tested the hospital populations to ascertain the probable maximum incidence of increases in IgM titers apt to arise from diseases associated with increased concentrations of serum IgM which might possibly have been present though unrecognized in the goitrous patients.

The upper normal limit of IgM concentration is considered to be about 150 mg/100 ml. Accordingly, an arbitrary upper limit of normal, 179 mg/100 ml, was set for the purpose of our study, and values in excess of this were considered to represent elevated concentrations. Approximately 15 of 160 pooled controls (10 percent) had serum concentrations in excess of this limit (Table 1). Of the controls, 33 were healthy subjects in the New York series. In this subgroup, 1 only of the 33 had an IgM concentration of 180 mg or more per 100 ml.

An upper limit of normal for IgG was arbitrarily set at 1999 mg per 100 ml of serum and 349 mg per 100 ml for IgA. Of the 160 controls, 28 (17 percent) had elevated IgG concentrations and 15 (9 percent) increased IgA concentrations. Concentrations of IgD were normal with one or two exceptions. Of the first 36 Finnish and Greek goitrous patients tested, seven had IgG concentrations in excess of the upper normal limit, and one each had an elevated IgA or IgD concentration. Since these values were almost identical with those of the controls, no further determinations of these immunoglobulins were made.

In contrast, half of patients from the areas endemic for goiter, including the cretins tested (Table 1), had increased IgM. Chi-square values (Table 2) for the differences from control are highly significant whether comparison is made with the controls living in nearby areas of iodine abundance ($P < .001$) or with the total number of controls including those in New York City ($P < .001$).

Of 40 patients studied in New York City with sporadic nontoxic nodular goiter, 16 (40 percent) had IgM titers of 180 or more. The chi-square value of the difference from the control groups is 24.3 ($P < .001$).

Elevation of circulating IgM concentrations in about half of patients from iodine-deficient areas endemic for goiter and from areas of iodine abundance with sporadic nontoxic goiter is statistically highly significant compared to the values in control patients without known thyroid disease. This incidence resembles that for increase in titers of antibody to thyroglobulin in endemic goiter reported by Höfer and Schatz (*4*) and by Soto *et al.* (*5*) and raises the question of an autoimmune event.

Circulating IgM concentrations have been reported to be elevated in a variety of conditions including early in the course of immunization and during certain infections, particularly rheumatoid arthritis (*8*), in sarcoidosis but not tuberculosis (*9*). Elevated concentrations have also been reported (*10*) in patients with eye changes (classes 2 to 6) of Graves' disease (*11*) and in other diseases. However, in Finland, Greece, and Germany the control populations living close to the corresponding endemic areas had essentially the same low incidence (10 percent) of elevated IgM as hospital patients in New York City (the incidence in the healthy subjects in the New York area was 3 percent); and the goitrous patients in the areas of endemia were considered healthy by the collecting physicians, except for the goiter. Thus, the likelihood that undetected disease accounts for the IgM increase seems small. Absence of complicating disease also is indicated by the fact that the percentages of goitrous patients with increased IgM concentrations were very close to those of patients with sporadic goiters from New York City.

Therefore the increased IgM concentrations are probably not irrelevant but seem related in some way to activation of the thyroid during goitrogenesis. The occurrence could be secondary to the goitrogenesis or could represent a defect related to a predisposition to form goiter. In addition, other mechanisms are suggested, such as delay in degradation of IgM or a disturbed balance between IgM production and removal of the thyroid, possibly related to alterations in the state of thyroid function or to the behavior of a thyroidal or nonthyroidal antigen.

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